SYNTHESIS OF SOME QUINOLINE AND PYRIDINE DERIVATIVES

BY

EARLE MARVIN VAN HEYNINGEN

A.B., Calvin College, 1943

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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PART ONE

PLASMOCID HOMOLOGS

I. Introduction

Clinical use has proved plasmocid, 8-(3-diethylaminopropylamino)-6-methoxyquinoline, to have toxic side reactions when administered as a suppressive in human malaria. It is possible that some structural modification of plasmocid might reduce its toxicity while retaining its activity. The compounds in which the modification is the substitution of a methylene or phenylene group between the quinoline ring and the basic side chain were therefore synthesized and tested.

II. Discussion of Results

The substitution of the amino group of 8-amino-6-methoxyquinoline by a chlorine atom in a modified Sandmeyer reaction (1) yielded 8-chloro-6-methoxyquinoline. The chlorine atom was replaced by a cyano group after the method of Craig (2) and the nitrile produced was reduced to 8-aminomethyl-6-methoxyquinoline. Treatment of this compound with 3-diethylaminopropyl chloride gave the methylene homolog of plasmocid, 8-(3-diethylaminopropylaminomethyl)-6-methoxyquinoline (S. N. 14,773). This drug when tested against avian malaria was shown to be inactive at the maximum tolerated dose.

The preparation of the ring system of the phenylog of plasmocid was by the Marsden modification of the diazo-reaction (3). The stabilized salt of diazotized 8-amino-6-methoxyquinoline with 1,5-naphthalenedisulfonic acid was catalytically decomposed in nitrobenzene to yield a mixture of isomeric 6-methoxy-8-nitrophenylquinolines. The pure *para* isomer was isolated and its structure proved by oxidation to *p*-nitrobenzoic acid. The mixture of nitro compounds was

reduced and the pure *para* amino isomer obtained; its identity with the reduction product of the pure *para* nitro isomer established its structure. Alkylation of the amine with 3-diethylaminopropyl chloride gave 8-(*p*-3-diethylaminopropylaminophenyl)-6-methoxyquinoline (S. N. 12,099).

PART TWO

A SYNTHESIS OF ENDOCHIN

I. Introduction

Endochin, 3-heptyl-4-hydroxy-7-methoxy-2-methylquinoline, was found by German experimenters to be a prophylactic and a cure for avian malaria. An independent research for a method of synthesis of this compound was undertaken to furnish a sufficient amount for testing in a check on the German claims.

II. Discussion of Results

Ethyl *n*-heptylacetoacetate was prepared by the method of Adkins and Wojcik (4). This ester was mixed with *m*-anisidine to produce ethyl α-carbethoxy-β-*m*-methoxyanilinocrotonate. The cyclization of the crotonate in refluxing diphenyl ether gave the desired drug. Although the conditions for the formation of the anilinocrotonate were varied, the best yield of endochin obtained was only 31 per cent. That the condensation between the acetoacetic ester and *m*-anisidine had not given an acetoacetanilide was proved by the preparation of the acetoacetanilide and its cyclization by the method of Knorr (5) to 3-heptyl-2-hydroxy-7-methoxy-2-methylquinoline.

PART THREE

THE SYNTHESIS OF 7-CHLORO-4-(4-DIETHYLAMINO-1-METHYLBUTYLAMINO)-5-METHOXYQUINOLINE

I. Introduction

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline (S. N. 7,618) has been found to be an excellent antimalarial drug (6). The present investigation was instigated to determine if the substitution of a methoxyl group in the five-position of the above drug would either enhance or mitigate its activity.

II. Discussion of Results

3-Chloro-5-methoxyaniline, prepared after the manner of Hodgson and Wignall (7), was condensed with ethoxymethylenemalonic ester and the anilinoacrylate formed was cyclized to 3-carbethoxy-7-chloro-4-hydroxy-5-methoxyquinoline (8). Saponification of this ester gave an acid that was thermally decarboxylated. The resulting 7-chloro-4-hydroxy-5-methoxyquinoline when treated with phosphorus pentachloride and phosphorus oxychloride yielded 4,7-dichloro-5-methoxyquinoline. When the chloroquinoline and noval diamine were heated together, 7-chloro-4-(4-diethylamino-1-methylbutylamino)5-methoxyquinoline was isolated. The structure was not proved. The drug was tested on ducklings and found to possess a quinine equivalent of 0.5 and a toxicity 1.2 times as great as that of S. N. 7,618.

PART FOUR

AN ATTEMPTED SYNTHESIS OF BRANCHED CHAIN DIAMINES

I. Introduction

Because straight chain diamines show only slight antimalarial activity in infrequent instances, a synthesis of some branched chain diamines was attempted to discover if chain branching would introduce activity in this type of drug.

II. Discussion of Results

4-Picoline was alkylated with *n*-amyl bromide by the method of Chichibabin (9) to yield 4-*n*-hexylpyridine. This alkylated pyridine was reduced to the corresponding piperidine and the piperidine in turn was treated with benzoyl chloride. Attempts to open the ring of N-benzoyl-4-*n*-hexylpiperidine by the method of von Braun (10) were unsuccessful and the synthesis of the diamines was abandoned at this point. A similar series of reactions on 4-*n*-amylpyridine gave like results.

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VITA

The author was born in Chicago, Illinois, on October 15, 1921. He attended the Englewood Christian School, graduating in 1935, and the Chicago Christian High School, graduating in June, 1939. In September of that year he matriculated in Calvin College, Grand Rapids, Michigan, and received the Bachelor of Arts degree in June, 1943. In that same month he enrolled in the Graduate School of the University of Illinois, where he held a teaching assistantship in chemistry. He continued in this capacity until May, 1944, when he joined the Antimalarial Program as a special research assistant.